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Original Article

Apheresis-Adverse Events in Man and Machine Individualities

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Abstract:

Adverse events due to platelet pheresis are not unheard of citrate related reactions being the most common. Most of these events are mild and self limiting. The current study describes adverse events in platelet pheresis using modern apheresis systems. This prospective study included 1455 platelet pheresis procedures done from July 2016 to December 2017. Procedures were performed on Hemonetics MCS+, Trima Accel and Cobe spectra cell separators. The endpoint of each procedure was a yield of 3 × 1011 platelets (PLTs) per unit. Donor adverse reaction if any was managed, reported, and documented. The median age of donors was 31 years with male to female ratio of 13:1. The median body surface area and body mass index were 1.64 m^2 and 22.4 kg/m^2, respectively. The mean PLT count of donors was 199.8 × 103/uL with a mean hemoglobin value of 13.6 g/dl. ACD infusion was significantly more in the Hemonetics MCS+, ($P< 0.01$). Donation time was least with the Trima compared to Hemonetics MCS+ ($P< 0.01$) and Cobe ($P< 0.001$). Total whole blood volume processed was higher in Hemonetics MCS+, ($P< 0.01$). Paresthesia due to citrate toxicity was the most common adverse reaction (65.3%), and vascular injury was observed in only five donors. The overall incidence of adverse reaction was 3.4%. Serious adverse events were not observed. The modern generation apheresis machines are more donors friendly and cause less adverse reactions compared to the older versions. Good donor screening, optimized donor physiognomic and hematological values and skilled operators are the key factors in reaction reduction by apheresis.

Key words: Apheresis.

Introduction:

Although platelet pheresis procedures are considered safe, adverse events related to these procedures have been discussed elaborately in the literature[1-2]. Donors suffer a mild reaction requiring no medical intervention. Apheresis procedures are commonly associated with citrate related reactions and comprise 30%-40% of all reactions.These reactions are generally transient and self-limiting. Other adverse events include hematoma, pain or swelling at the phlebotomy site, peripheral neuropathy, blood loss, hypertension and allergic reactions. Serious adverse events due to platelet pheresis such as severe vasovagal reactions, non vasovagal hypotension, neuropathy, syncope, angina or myocardial ischemia are rare and comprise only 0.16 to 0.24% of all reactions[2-6]. The possible effects of apheresis on a donor or a patient can be classified as physiological effects and adverse effects. The easily reversible physiological effects such as mild paresthesia and light headedness due to citrate infusion are an expected phenomenon that has trivial deviations from baseline physiology. Frequency of apheresis donor reactions varies from study to study, and the authors have also observed that almost all their donors experienced some form of physiological or adverse effects during or after the donation[2,3,7,8]. The current study describes adverse events in platelet pheresis using modern apheresis systems.

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Materials and Methods:

Donors and procedures

This was a prospective study that included 1455 platelet pheresis procedures performed on eligible donors from July 2016 to December 2017. All procedures were performed by the same apheresis team after taking informed consent. No prophylactic calcium supplementation was administered to any donors. A total of 561 procedures were performed on Hemonetics MCS+, 679 on Trima Accel cell separator (version 5.1, Terumo BCT, Lake wood, USA), and 215 using the

Cobespectra cell separator (version 7.0LR Sturbo, Terumo BCT, Lake wood, USA). All these procedures were performed using closed-system apheresis kits and acid citrate dextrose (ACD) with anticoagulant in the proportion of 1:10-1:12. The end point of each procedure was based on the target yield of 3×1011platelets (PLTs) per unit. Procedure summary including donor and platelet pheresis details, patient details, donor reaction if any, reaction management, and quality of product obtained was recorded in the departmental procedure register.

Measurements

As a part of the screening process, pre donation hematological values of all donors, such as PLTs, hemoglobin (Hb), hematocrit, and white blood cell count, were measured using a routinely calibrated automated cell counter.

Reporting and documenting donor reactions: Procedure details were explained to the donors and all were directed to report any form of discomfort or uneasiness immediately to the apheresis team. Donors were also observed for any specific significant reactions. Any donor reaction, physiologic or adverse, was reported accordingly, and details of each reaction including its management were documented and notified to medical officer in charge of apheresis section.

Statistical analysis

Statistical analysis was performed using the SPSS statistical package (IBM, SPSS, Version14, USA). All results were calculated as mean±standard deviation, and $P<0.05$ was considered statistically significant.

Results:

The median age of platelet pheresis donors was 31years with male-to-female ratio of 13:1. The median body surface area and body mass index were calculated to be 1.64m^2 and 22.4kg/m^2, respectively. The mean pre-apheresis PLT count of the donor population was199.8×103/uL with a mean Hb value of 13.6g/dl [Table I].

Table I also describes the procedure-related factors in platelet pheresis. ACD infusion was significantly more in the Hemonetics MCS+ (351ml) compared to Cobe spectra (269.7ml) or Trima (290ml; $P<0.01$). Donation time was least with the Trima (63.3min) and the value was significantly lower compared to Hemonetics MCS+(69.3min; $P<0.01$) and Cobe (77.3min; $P<0.001$). Total whole blood volume processed was higher in Hemonetics MCS+ (3557.3ml) compared to the other two machines ($P<0.01$). Table II depicts the adverse reaction during or after platelet pheresis. Where paresthesia due to citrate toxicity was the most common adverse reaction (32/49, 65.3%), vascular injury was observed in only five donors. Adverse reaction was significantly more with the Cobe (5.6%) compared to Hemonetics MCS+ (3.6%) and Trima (2.5% ; $P<0.01$). In the present study, the overall incidence of adverse reaction in platelet pheresis was 3.4%.

Table I: Donor demography, hematological values & procedural factors in platelet pheresis (n=1455)

Demography			
Parameters	Cobe(n=215)	Hemonetics MCS+(n=561)	Trima(n=679)
Age (range)	30 (21-51)	39 (19-55)	36 (19-55)
Gender (M: F)	17:1	9:1	18:1
Weight (kg)	63.4±9.25	66.4±11.4	64.3±12.03
Height (m)	1.61±3.2	1.64±2.7	1.61±2.9
TBV(ml)	M:4543±434, F:3677±402	M:4667±397, F:3616±356	M:4728±420, F:3507±422
Hematological value			
Platelet count ($\times10^3$/uL)	207±43.12	196±63.45	201±49.76
WBC count ($\times10^3$/uL)	7.9±1.59	8.5±1.77	8.1±1.56
Hb(gm/dl)	13.7±1.23	13.3±1.31	13.1±1.25
Hct(%)	40.7±2.98	42.1±3.10	41.9±3.22
Procedure related factors			
Vein access	**Double**	**Single**	**Single**
ACD:WB	1:10	1:11	1:11
ACD(ml)	351.3:37.8	269.7±59.6[a]	290±78.3[a]
DT(min)	77.3:19.3	69.3±15.6[a]	63.3±12.8[a]
WBP(ml)	3557.3:312.1	2452.3±663.9[a]	2760.9±787.8[a]

All values expressed as mean±SD. a Significant compared with Cobe

Table II: Adverse reactions in platelet pheresis (n=1455)

Adverse Reactions	Cobe (*n*=215)	Hemonetics MCS+(*n*=561)	Trima (*n*= 679)	Total (%)
Citrate toxicity	5	13	14	32(65.3)
Flushing, Nausea	3	3	1	7(14.3)
Syncope, Vasovagal episodes with <60 heart rate	3	2	1	6(12.3)
Vascular injury	2	2	1	5(10.2)
Total (%)	12(5.6)	20(3.6)[a]	17(2.5)[a]	49(3.4)

a= Significant compared with Cobe

Discussion:

Data with regard to donor adverse effects in platelet pheresis vary from center to center despite using the modern apheresis instruments. Donor demographic and physiological profiles probably play important roles[2,8,9]. We observed that factors such as low normal PLT counts, average donor built, and average total blood volume necessitate high blood volume processing and high donor anticoagulant infusion to achieve the target yield of 3×10^{11} PLTs per unit. All these may contribute to donor adverse effects in platelet pheresis significantly. None of the 105 female donors had any adverse event despite being first time donors and mean weight of 52kg. This may be attributed to high PLT count (mean:266×10^3/uL) demonstrated in our female donors, which reduced the donation time (57.9min vs. 69.3min, P<0.001) and anticoagulant utilization (249ml vs. 291ml, P<0.01) significantly.

Where a total of 4497 healthy donors were screened for eligible platelet pheresis, 1957 (43%) donors were selected. Most of the male donors were deferred due to low PLT count and poor venous access. The most common cause of male deferral was anemia. Female donors could withstand procedure well compared to male donors. ACD infusion was significantly more in the Hemonetics MCS+ machine compared to Cobe spectra or Trima (P<0.01). Donation time was least with the Trima machine and the value was significantly lower compared to Hemonetics MCS+ (P<0.01) and Cobe (P<0.001). Total whole blood volume processed was higher in the Cobe compared to the other two machines (P<0.01). Similar observation was depicted by Tendulkar and Rajadhyaksha where total blood volume processed and donation time were higher in the Hemonetics MCS+compared to Amicus. While anticoagulant usage was higher with the Hemonetics MCS+in the current study, Tendulkar and Rajadhyaksha observed anticoagulant use with the Cobe compared to Amicus[10]. In another study by Keklik et al., the Trima and Amicus were comparable with regard to all parameters, except PLT yield and collection efficiency which was better with the Trima compared to Hemonetics MCS+[11].

The present study observed paresthesia or perioral tingling sensation due to hypocalcemia as the most common adverse reaction, and this was observed in 32 donors which constituted 65.3% of the total adverse reactions. Other reactions included nausea and flushing (14.3%), vasovagal episodes (12.2%), and vascular injury such as hematoma or arm pain (10.2%). None of the donors with citrate-related reactions needed intravenous therapy and were managed with oral elemental calcium in a dose of 1-1.5g. Adverse reactions were observed more with Hemonetics MCS+ and this can be attributed to processing of significantly high whole blood volume and infusion of increased ACD with long donation time. To prevent future paresthesia and citrate toxicity due to hypocalcemia, we started prophylactic 500mg chewable oral elemental calcium before all platelet pheresis procedures since August 2016. Of the 197 PLT donations from August 2016 to December 2017, citrate toxicity in the form of perioral tingling was observed in 1healthy donor. This definitely suggests the therapeutic benefit of prophylactic calcium supplement before platelet pheresis.

In context to Indian studies, Philip et al observed 85 adverse reactions in 3120 platelet pheresis procedures with majority (52.61%) complaining of vascular injury. Citrate reactions were observed in 30 donors[9]. In contrast, the current study witnessed more citrate-related reactions than vasovagal reactions or vascular injury. However, majority of vascular injury can be prevented by good vein selection and skilled phlebotomist. Donor inattentiveness and excessive arm movement may cause vascular injury. In a multicentric study by McLeod et al. 2.18% of platelet pheresis donors suffered acute adverse reaction; most of the reactions were associated with the Hemonetics cell separator[3].

While volume of ACD-usage varies with cell separators, the modern separators have been observed to utilize less anticoagulant compared to the older machines. Moreover, extracorporeal volume in modern machines is much lower than the older machine which controls the volume of blood returned to the donor, thereby enhancing adequate blood dilution throughout total extracellular fluid of the donor. Second, the body gets sufficient time to metabolize infused citrate and release the bound calcium[6]. Despite modernization and

equipment optimization, citrate-related reactions are the most common adverse events in platelet pheresis. These are due to donor individuality and variable biological and physiological donor characteristics. Das et al. depicted that hypocalcemia-like symptoms may be caused by hypomagnesemia and the authors observed significant lowering of ionized magnesium after platelet pheresis. Such situation at times may be misdiagnosed and calcium supplementation becomes unfruitful[12]. Crocco et al concluded that 0.3% of their whole blood and apheresis donors were complicated by adverse events; most of these reactions were mild and did not necessitate hospitalization. They reported citrate toxicity and vasovagal reactions in189 (0.38%) and 124 (0.24%) apheresis donors, respectively[13]. In the contrary, Leanes et al. observed that 53% of the adverse reactions were vascular injury followed by vasovagal (23.7%), lipemia (10.3%), and citrate reactions (5%)[14]. In the present study, most reactions were mild, except one low-weight (54kg) male donor who needed help from the emergency team for prolonged vasovagal symptoms and nausea. Of 15,763 platelet pheresis procedures performed by Yuan et al. using the Trima Accel cell separator, 59(0.37%) donors suffered adverse reactions, the most common reaction being presyncopal or syncopal episode (32.2%)[15]. Winters JL concluded that the most common apheresis-specific reaction is hypocalcemia due to citrate anticoagulation which is usually mild but at times has potential for injuring the donors severely[8].

Conclusion:

We concluded that modern-generation apheresis machines are more donor-friendly and cause less adverse reactions compared to the older versions. In addition, good donor screening, optimized donor physiognomic and hematological values, and skilled operator are the key factors to reaction reduction by apheresis.

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